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ORIGINAL ARTICLE

# Effects of prophylactic antibiotics in acute pancreatitis

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## Abstract

**Objectives:** The use of prophylactic antibiotics in severe acute pancreatitis (SAP) is controversial. The aim of this study was to compare the effects of antibiotics administered as prophylaxis and as treatment on demand, respectively, in two prospective, non-randomized cohorts of patients.

**Methods:** The study population consisted of 210 patients treated for SAP. In Group 1 ($n = 103$), patients received prophylactic antibiotics (ciprofloxacin, metronidazole). In Group 2 ($n = 107$), patients were treated on demand. Ultrasound-guided drainage and/or surgical debridement of infected necrosis were performed when the presence of infected pancreatic necrosis was demonstrated. The primary endpoints were infectious complication rate, need for and timing of surgical interventions, incidence of nosocomial infections and mortality rate.

**Results:** Ultrasound-guided fine needle aspiration [in 18 (16.8%) vs. 13 (12.6%) patients; $P = 0.714$], ultrasound-guided drainage [in 15 (14.0%) vs. six (5.8%) patients; $P = 0.065$] and open surgical necrosectomy [in 10 (9.3%) vs. five (4.9%) patients; $P = 0.206$] were performed more frequently and earlier [at 16.6 ± 7.8 days vs. 17.2 ± 6.7 days ($P = 0.723$); at 19.5 ± 9.4 days vs. 24.5 ± 14.2 days ($P = 0.498$), and at 22.6 ± 13.5 days vs. 26.7 ± 18.1 days ($P = 0.826$), respectively] in Group 2 compared with Group 1. There were no significant differences between groups in mortality and duration of stay in the surgical ward or intensive care unit.

**Conclusions:** The results of this study support the suggestion that the use of prophylactic antibiotics does not affect mortality rate, but may decrease the need for interventional and surgical management, and lower the number of reoperations.

## Keywords

acute pancreatitis, antibiotic prophylaxis, treatment, outcomes, infected necrosis, surgical management

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## Introduction

Annual incidences of acute pancreatitis (AP) are reported to range from five to 80 cases per 100 000 population.[1–3] This wide variation in incidence reflects several factors, including: population differences; dominant aetiology (alcohol abuse, biliary stone disease, etc.), and variations in clinical assessment.[3,4] Overall mortality rates are between 10% and 20% and can reach 50% in patients with severe acute necrotizing pancreatitis.[5,6] Persistent organ failure and uncontrolled systemic inflammatory response syndrome are associated with the highest mortality rates during the first weeks of the disease.[6,7] Secondary pancreatic infection, which usually develops from the third week after the onset of AP, may affect up to 40–70% of patients with pancreatic necrosis exceeding 30%.[7–9]

In most patients, bacteria complicating acute necrotizing pancreatitis originate from the gastrointestinal tract and include *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Bacteroides* spp. and *Clostridium* spp.[10,11] Some recent research has reported a rising incidence of fungal infection (*Candida* spp.) of up to 35%.[12] Despite some clinical and experimental studies, the pathogenesis of secondary infection

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of the necrotic pancreas remains unclear; however, some evidence supports the hypothesis that such infection represents the translocation of a microorganism from the gastrointestinal tract.[10,13,14] Haematogenous dissemination, ascending infection caused by reflux into the pancreatic duct, the migration of microorganisms via the lymphatic system or a combination of these factors are the likely point of entry.[15,16]

The prophylactic use of antibiotics to reduce the rate of secondary infection of pancreatic tissue, systemic infectious complications and mortality rates remains controversial.[16–18] Broad-spectrum antibiotics that achieve a minimum inhibitory concentration (MIC) in necrotic pancreatic tissue are needed if antibiotics are to be successful in clinical practice.[7,12,19]

A number of experimental and clinical studies evaluating the benefit of antimicrobial prophylaxis to prevent secondary infection of pancreatic necrosis have been published within the last decade.[17,18,20–27] However, there is still no unanimous agreement as to whether prophylactic antibiotics should be used routinely. The aim of this study was to compare the effects of antibiotic prophylaxis with the effects of antibiotic treatment administered on demand in two prospective, non-randomized cohorts of patients.

## Materials and methods

### Study design and patient population

This was a prospective, non-randomized, single-centre, cohort study. The study was approved by the regional ethics committee. All patients provided written informed consent. Prospective data collection was performed at the Department of Surgery, Lithuanian University of Health Sciences using a specially developed and maintained database from 1 January 2005 to 1 March 2010. All patients admitted to the Department of Surgery or transferred from other institutions with predicted severe and/or necrotizing severe acute pancreatitis (SAP) for which the onset of disease occurred within the previous 72 h were eligible for inclusion in the study ($n = 210$). The diagnosis of SAP was based on clinical symptoms (abdominal pain, nausea and vomiting), elevation of serum α-amylase greater than three times the normal level, and either or both of the following characteristics: C-reactive protein (CRP) of > 120 mg/l, and a clinical picture of SAP as demonstrated by an APACHE II (acute physiology and chronic health evaluation II) score of > 7. The presence of pancreatic necrosis was confirmed and its volume assessed by contrast-enhanced computed tomography (CT) performed at 5–7 days after the onset of disease, even if CT had been performed on admission. Two different scoring systems were consistently employed to assess the severity of AP on admission and during follow-up: APACHE II, and MODS (multiple organ dysfunction syndrome).

The study timeframe was divided into two distinct periods, characterized by the different treatment strategies utilized in each. A total of 103 patients (Group 1), admitted to the surgical ward from 1 January 2005 to 31 January 2007, were routinely given antibiotic prophylaxis (ciprofloxacin 800 mg/day, metronidazole 1500 mg/day for 14 days) if at least one of the following indications was present within the first 72 h from the onset of disease: CRP > 120 mg/l; APACHE II score > 7, and/or necrosis of > 30% as demonstrated on contrast-enhanced CT.

During the period from 1 January 2008 to 31 December 2009, a total of 107 patients (Group 2), admitted to the surgical ward based on the same criteria, received no prophylactic antibiotic treatment because meta-analyses published in the period from 2003 to 2008 demonstrated no clear benefit of antibiotic prophylaxis in the management of SAP.[14,18,28] Instead, patients in this group were treated on demand with i.v. antibiotics according to bacterial culture results.

Patients treated during the period from 1 February 2007 to 31 December 2007 were deliberately excluded from the statistical analysis because this was a transitional period during which the follow-up and management protocol of patients with AP remained essentially the same as those applied during the period from 1 January 2005 to 31 January 2007, but antibiotic prophylaxis was gradually withdrawn from routine clinical practice. The only change to the former protocol other than that to antibiotic prophylaxis was that patients diagnosed with SAP were routinely monitored for intra-abdominal pressure (IAP) starting from May 2007. At that time, a study had been initiated to assess the value of widely used clinical scores in the early identification of AP patients who were likely to suffer from intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS).[29] In the context of this study, the feasibility and effectiveness of subcutaneous fasciotomy of the anterior rectus abdominis sheath were assessed, as well as the role of ultrasound (US)-guided drainage of intra-abdominal and peripancreatic fluid collections in the management of ACS.[30] However, Group 1 patients were not routinely monitored for elevated IAP.

All patients included in the current study were continuously monitored until discharge. A septic condition or extrapancreatic organ failure were considered as indications to obtain bacterial cultures from peripancreatic fluid collections, blood, urine, sputum and/or tracheal aspirate. Ultrasound-guided fine needle aspiration (FNA) was performed in all patients in whom pancreatic necrosis had been confirmed by CT and in whom persisting symptoms of SAP (APACHE II score > 7 or failure of at least one extrapancreatic organ) and/or signs of sepsis (usually not earlier than week 2 after the onset of disease) were apparent. When infection was demonstrated, US-guided drainage, or retroperitoneoscopic or surgical debridement of infected necrosis was performed. A minimally invasive step-up approach was used throughout the entire study period. Percutaneous drainage was performed in all patients as a first step, whereas retroperitoneoscopic or open surgical debridement (depending on the size and accessibility of the infected collection) was reserved only for patients in whom no improvement was seen after percutaneous drainage. A septic condition (sepsis) in the current study was defined as acute organ dysfunction secondary to infection and/or septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation).


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